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Human Recombinant Erythropoietin: Progress in Clinical Development

Ludzka rekombinowana erytropoetyna: postęp w badaniach klinicznych

The production of recombinant human erythropoietin (r-Hu EPO) has been a major breakthrough in the management of patients with anemia secondary to end-stage renal failure. The successful and safe use or r-Hu EPO in the treatment of the anemia of chronic renal failure (CRF) has been well documented. Over the last few years r-Hu EPO has been tested in other types of anemia. Beyond the simple lack of endogenous erythropoietin (EPO) in CRF, it has proved more difficult to identify other patients population for the therapy and to select the optimal dose and regimen for treatment. In planning new strategies for use of r-Hu EPO it is helpful to remember the three categories of therapy listed in Table 1. Obviously different doses and scheduling are necessary in each category.

Table 1. Categories of r-HuEPO therapy

1. Replacement or additive (e.g. endogenous level not adequate)
2. To overcome inhibitory factors or drugs (e.g. malignant disease/chemotherapy)
3. To enhance normal erythropoiesis (e.g. for autotransfusion)

ERYTHROPOIETIN PATHOPHYSIOLOGY

The function of EPO is to adjust the red cell mass to the optimal size in order to satisfy the oxygen requirement of the body. The amount of circulating EPO is regulated by oxygen sensor in the kidney through feedback signals. EPO is now thought to be produced, in part or even exclusively, by the interstitial cells of the kidney, in a peritubular location, out of the glomeruli and out of the tubules. Besides the kidney, the liver in both fetal and adult life is a well-established

extrarenal site of hormone production. The local production of EPO by subpopulation of macrophages in the bone marrow (BM) is to be of local improtance. EPO acts by controlling the differentiation of eythroid progenitor cells in the BM. Erythroid cells acquire EPO sensitivity between the primitive burst-forming unit-erythroid (BFU-E) and the mature BFU-E stages (eg. CFU-E) and lose sensitivity after the proerythroblast stage, but before reticulocyte formation. Possible modes of EPO action at the cellular level include stimulating mitosis, directing a program of terminal differentiation, and permitting survival. During normal erythropoiesis, EPO permits the survival of only a minority of the EPO-dependent progenitor cells. However, when EPO concentrations are elevated due to anemia or some other cause of tissue hypoxia, many of the EPO-dependent progenitors that would normally die can survive, differentiate, give rise to reticulocyte, and thereby increase red blood cells (RBC) production. Conversely, when EPO concentrations are decreased below normal due to renal disease, starvation or hypertransfusion, some of the EPO-dependent progenitor cells that would survive at normal EPO concentrations will die due to insufficient EPO and thereby reduce RBC production. Research in patients with iron-deficiency, anemia has revealed that EPO levels do rise in response to a decreasing hematocrit (Ht), but only when the hematocrit falls below 32%. At that point, EPO becomes a useful marker for assessing whether a patient's BM is responding appropriately. In anemia the serum EPO concentration, which is normally around 15 U/l, can increase 1000-fold, or even more. It has also happened in patients with CRF – whether they are anephric or not, these individuals often have adequate levels of EPO. The reason why a patient with „normal" EPO level can be anemic, appears to be that these individuals cannot raise their EPO concentration high enough to „turn on" the bone marrow. Patients who do not exhibit appropriate increases in serum EPO level for a given decrease in hematocrit include those with rheumatoid arthritis and chronic inflammation, chronic infection (e.g. AIDS), cancer, diabetes and alcoholism. To identify and select patients for r-Hu EPO therapy it is necessary to categorize them in terms of magnitude and type of erythropoietic deficiency (Table 2.)

Table 2. Classification of endogenous EPO deficiency

1. Primary or acquired
2. Permanent or temporary (e.g. prematurity)
3. Sole factor or complex factors (e.g. cancer plus chemotherapy)
4. Drug treatment or no drug treatment (e.g. platinum or not)
5. Inhibitory or negative factors present or not (e.g. high α TNF or other cytokinin blocking EPO)
   (damaged red cell stem cells – e.g. severe MDS)

ANEMIA OF CHRONIC INFLAMMATORY DISORDERS

Anemia is a frequent complication in patients with chronic inflammation caused by, e.g., infectious diseases including the acquired immunodeficiency syndrome (AIDS), autoimmune diseases such as rheumatoid arthritis or

inflammatory bowel disease, and malignant diseases. Chronic inflammatory disorders (CID) are often associated with multifold disturbances of cell-mediated immunity. *In vivo* obtaining data agree with *in vitro* experiments demonstrating the capacity of cytotoxic T cells and specific cytokines such as interferon γ (INF γ) and tumor necrosis factor α (TNF α) to inhibit bone marrow hematopoiesis. Inflammation results in hypoferremia, and hemoglobin concentration correlates to the availability of iron in patients. A parallel increase of serum ferritin and of iron in reticuloendothelial cells can be observed. Thus decrease in serum iron appears to result from an active transfer of serum iron into storage sites. Iron is retained by the activated mononuclear phagocyte system, which results in an impaired iron availability in the bone marrow. Due to cytokinins realizing and disregulation related to inflammatory process, the synthesis of both ferritin and lactoferrin is increased. Throughout their iron binding properties, these proteins may also contribute to a lower bone marrow iron availability. Iron metabolism and anemia severity are also influenced by interleukin 1 (IL 1), by neopterin realizing. Chronic immune activation, which is reflected by increased neopterin level, is associated with depletion of iron from the circulation, whereas the storage protein ferritin is increased. Ferritin itself suppresses hematopoietic progenitor cell proliferation and thus can further contribute to the development of anemia. However, the mechanism of anemia of chronic disorders (ACD) is much more complicated and still unclear, there is no doubt about the fact, that chronic inflammation is associated with enhanced endogenous realizing of cytokinins which, in turn, induce changes of iron metabolism and decrease of Hb in patients.

Generally, ACD EPO concentration raises in order to stimulate erythropoiesis if renal function is adequate. But it may be that EPO concentrations are higher but the titres are insufficient to overcome the anemia. It is also postulated that the target, erythroblastoid, EPO sensitivity is impaired in patient with ADC. Especially. Il 1 and TNF α may cause a decreased in erythroblast – erythropoietin sensitivity in patients. Thus the r-Hu EPO treatment is a potential approach to ACD. Its value is fully established in the treatment of malignancy induced anemia, HIV positive patients when treated by zidovudine, in rheumatoid arthritis and other inflammatory disorders.

r-Hu EPO IN CANCER PATIENTS

Anemia of malignancy is of multifactorial origin, but could be divided into 2 categories: hyper- and hyporegenerative. Hyperregenerative anemia includes hemolytic and posthemorrhagic anemia, whilst hyporegenerative anemia includes carential anemia, myelophthisic and sideroblastic anemia, primary and secondary aplastic anemia and the „anemia of malignancy" not included in any of the previous entities. The presence and severity of anemia usually reflects the severity of the neoplastic disease. It is almost universally present in patients with disseminated malignant tumor or hematological malignancy. In non-metastatic stages, the incidence of anemia depends both on the primary site and the tumor

burden. It is evident that anemic patients poorly tolerate intensive antitumor therapies. The correction of anemia is essential before starting tumor therapy and before diagnostic surgery, particularly as the surgery and the majority of anticancer treatments will also induce anemia. During anemia red cell precursors may be recruited into cell cycle and subsequent exposition to cytotoxic agents could kill a significant proportion of these cells, further exacerbating the degree of anemia. Cisplatin is one of the drugs that induces severe anemia. In addition to direct inhibition of erythroid precursors, the drug induces decrease in EPO concentration by inhibition of EPO production sites. What is important, the mechanism of anemia of malignancy is a ACD-type origin and is connected with cytokinins disregulation. A survey study of endogenous serum EPO levels in hospitalized patients with the anemia associated with cancer, has shown an inadequate EPO response for the degree of anemia when compared with patients with iron-deficient anemia. Most patients with cancer will require blood transfusions at some point, to correct anemia, which may be exacerbated by chemotherapy, and to prepare for surgery. But the blood transfusion ca be associated with:

- transfusion reactions,
- heart failure in patients with poor cardiac reserve,
- iron overload,
- infection with hepatitis (HBV, HCV) HIV and cytomegalovirus,
- further intolerance of allogeneic transplantation of BM,
- immune suppression.

The immunosuppresive effect of homologous blood transfusion is of major concern in oncology since the control of malignant disease may be modified by the immune system. This findings provide a theoretical basis further supporting the use of r-Hu EPO for the treatment of anemia in the cancer patients. Within the oncological field, r-Hu EPO could be used in the patient:

1. receiving cisplatin derivatives containing chemotherapy regimens,
2. all other cancer patients treated with chemo- or radiotherapy,
3. in which diagnostic/therapeutic surgical procedure will be necessary.

The results of open and comparative studies showed a significant increase in hematocrit values in all three groups of patients. Reduced need for transfusions was observed in recently performed trials, when relatively high does of r-Hu EPO (200-300 IU/kg, 3 × week) were used. Administration of the drug seems to be safe and well tolerated by the majority of patients. The virtual absence of toxicity makes r-Hu EPO very attractive for use in the treatment of the anemia of malignancy. Higher doses of r-Hu EPO resulted in decreased need for transfusions of packed red blood cells. Every patient improved life quality and showed better toleration of chemo- or radiotherapy. This effect was seen especially during the 2nd and 3rd month of therapy. Patients with solid tumors and hematologic malignancies appear to respond equivalently ro r-Hu EPO as did patients with or without tumor infiltration of the BM. Predictive factors of response to treatment in subsets of patients are still unfavorable. As it was proved in some studies, in group 3 r-Hu EPO could be a significant parameter in avoiding exposure to the risk (particularly the immunosuppressive effect) of

homologous blood transfusions, correcting the anemia and allowing the collection of sufficient autologous units to cover surgical needs. Cancer is generally considered an absolute contraindication to intraoperative salvage and consequently the only feasible technique in these patients is the collection of autologous units before operation. Without r-Hu EPO collection of autologous units is generally difficult in cancer patients because anemia can be a complication of the primary disease.

Future trials of combination of r-Hu EPO with other growth factors (CSFs) are also to be of great interest, since the hormone is known to have a synergistic effect with other CSFs in vitro and combined use in vivo may enhance its therapeutic effect. It is particularly important in recovery therapy after BM transplantation procedure.

r-Hu EPO IN AIDS

Anemia in AIDS and HIV infected patients may be the result of decreased RBC production, increased RBC destruction and blood loss. The HIV itself is responsible for the earliest signs of anemia, which occur well before the appearance of any other infection, inflammation or neoplasm. HIV-related complexes are expressed on the surface of the infected committed and progenitor RBCs and react with circulating HIV antibody to suppress proliferation of erythroblast. The most important, but not the sole mechanism, is ACD. At least two mechanisms are responsible for ACD. One is a result of cytokinins disregulation and iron metabolism distrubances, mediated by lactoferritin and tranferrin, which do not realize iron to developing RBCs. A second mechanism is the relative lack of EPO. For any given level of anemia, there is less EPO present than would be usually expected. EPO insufficiency leads to under-stimulation of the bone marrow and decreased erythropoiesis. Among other factors, which are contributive to anemia, such as:

- opportunistic infections and their treatment (e.g. Pneumocystosis and cotrimoxazole)
- direct erythroblastopenic effect of CMV and parvovirus infection
- increased RBC destruction and blood losses
- nutritional distrubances and vit. B12 deficiency
- existing of inhibitors to erythropoiesis (INFs, etc.)

the most important seems to be the additional treatment with zidovudine (AZT). It is a potent inhibitor of erythropoiesis, responsible even for the anemic crisis, observed during the therapy. AZT's hematologic toxicity is of great importance. The results of several clinical r-Hu EPO trials show reduced need for transfusions, increase in Hct, significant improvement in quality of life and better infection control. Apart from the fact, that Eprex is approved of by FDA for HIV positive patients treated with AZT whose EPO level is below 500 mU/ml (well responding to normal, therapeutical doses of r-Hu EPO), dose escalating studies are carried out. They are to determine if r-Hu EPO can overcome the anemia in patient with EPO level above 500 mU/ml. Preliminary results are

promising. A significant improvement in quality of life, work capacity are observed in both groups of patients. Even in high doses Eprex caused virtually no toxicity.

r-Hu EPO AND AUTOAGRESSIVE INFLAMMATORY DISORDERS

Finally, both previous and recent work showed that r-Hu EPO can be used to correct mild to moderate anemia that frequently accompanied rheumatoid arthritis. As the mechanism of anemia is a typical mechanism of ACD, r-Hu EPO is used to overcome relative lack of native EPO and inhibition of BM, which are the result of inflammatory processes. Correction of the anemia, improved work capacity and significantly improved quality of life and exercise tolerance have been observed during the studies. The doses of r-Hu EPO necessary to obtain increase in Hb level are higher then used in CRF patients, but – in contrast to them – are very well tolerated. The principle results of scientific works may prove that r-Hu EPO may be effective in a wide variety of patients undergoing autoagressive disorders (e.g. inflammatory bowel disease).

r-Hu EPO AND ANEMIA OF PREMATURITY AND POSTPARTUM ANEMIA

The anemia of prematurity is a self-limiting process lasting 1-3 months and characterized by anemia, low reticulocyte count, decreased erythroid activity in the bone marrow and low concentration of circulating EPO. During this period there is little or no rise in EPO in response to anemia, even when it is severe enough to become symptomatic and require transfusions. The more prematurely born the infant, the more severe and long-lasting the condition. The progressively increasing survival rate of smaller premature infants provides an increasingly important problem. For the time being, neonatal intensive care units are among the most frequent users of blood products, and anemia of prematurity is one of the major cuases of high rates of transfusions.

The fetus lives in a relatively hypoxic environment, and the Hct increases from about 40 to 50% between the second and third trimester in humans. The other compensation for the relative hypoxia *in utero* is the predominant synthesis of Hb F, which has a left-shifted oxygen dissociation curve. Fetal erythropoiesis is regulated by EPO synthesized in the fetal liver. Congenitally anepheric fetuses are born with essentially normal concentrations of EPO and Hb and normal Hct. A major effect on the infant's Hct level during the first weeks of infant's life has the transfusion of blood from the placenta. The newborn infant has a high reticulocyte count and moderately high EPO concetration. In the first days after birth, EPO falls to very low concentrations as to reticulocyte count and bone morrow erythroid activity decreases. In the full-term infants, this low level of erythropoiesis lasts for 1-2 months and the Hct gradually declines. Then EPO concentrations rise followed by a rise in reticulocyte count and Hct stabilizes. When erythropoiesis recommences, the switch from γ (HbF) to β chain synthesis

is almost completed. This process is prolonged in pre-term infants. Anemia is more severe and there is little erythropoietic response even when the anemia is severe enough to require transfusions. There are also several factors which tend to worsen the anemia of prematurity (e.g. shorter red blood cell survival, cardiopulmonary disease, intensive treatment and blood sampling, infections etc.). Premature infants tend to have lower Hct level at birth because of the progressive rise in Hct that occurs late in gestation. Extremely rapid post gestational growth needs proportionally increased blood volume. An early anemia is iatrogenic and occurs as a result of blood sampling. When it required blood transfusions, they can suppress the recovery from anemia of prematurity (HbA) gave better oxidation and worses recovery from anemia). The presence of anemia, responsiveness of newborn erythroid progenitors (BFU-E) to EPO and low EPO concentrations (100-1000-fold lower concentration of EPO in premature vs. term borne infants), suggested that r-Hu EPO therapy might be useful in premature infants. The long term goal of the performed clinical trials is to produce transfusion free premature infants. The achievement of this goal will yield important benefits for these infants and their parents, improve the physician's ability to manage this population, and preserve scarce blood resources. The most important benefit or r-Hu EPO therapy is a reduction in the number of transfusions given. Apart from the fact that there is still a number of questions to be answered (e.g. what are the nutritonal, particularly for iron, consequences of therapy?; how soon after birth can effective therapy be started? etc.), therapy is safe even when relatively high doses are required. The role of r-Hu EPO therapy for anemia of prematurity needs to be still explored.

There are few clinical studies available on r-Hu EPO treatment for postpartum anemia. The few existing ones show a rapid rise in Hb values, with a speeded recovery from anemia, showing that r-Hu EPO indeed is a serious alternative to the traditional iron supplementation. Recovery from postpartum anemia under iron supplementation may take up to 6 weeks, during which the newly-become mother can be incapable of living up to the demanding responsibilites of caring for a new-born baby. Due to the high risk of infections associated with blood transfusion, mothers are reluctant to receive this type of treatment. Therefore at present several pilot studies on r-Hu EPO in the treatment of postpartum anemia are carried out. An interesting positive fact in administration of r-Hu EPO is that estimated total dose of 20'000 IU of Eprex per patient costs about the equivalent of three blood transfusions (in western countries). The use of r-Hu EPO in obstetrics should be limited to the postpartum period since there are no definite results regarding placental permeability of r-Hu EPO during pregnancy to date.

r-Hu EPO IN BLOOD DONATION

The risk of homologous is well known, and it has been estimated that 20% of all transfused units of blood in western countries result in adverse effects. In Poland still the most important are infectious complications: transmission of

HBV and growing importance and incidence of HCV, risk of HIV infection transmission and for transplanted – CMV. Another major and lately of the great importance prolbem is the limited amount of available blood units. The advantages of autologous blood donations are well known, but the only disadvantage is the requirement of up to 5 weks of preoperational donation to yield an average of 2.2 units of blood per patients. Potential problem limiting sufficient autologous blood procurement include the EPO response to phlebotomy. Studies on iron deficiency anemia show that endogenous EPO level rise in a linear relationship to the degree of anemia for Hb value $< 11,5$ g%. Above this level there is no linear relationship, indicating that significant level of anemia is required to stiumulate endogenous EPO production. Since an iatrogenic anemia induced by phlebotomy induces only a mild anemia, there is an inadequate EPO response not compensating for blood loss. The fact that the endogenous EPO response is inadequate for the degree of anemia produced by phlebotomy justifies the use of r-Hu EPO. Several studies have shown a distinct advantage in using r-Hu EPO in predonation programs and in perisurgical settings with acute blood loss. The results of majority of performed studies showed that the amount of collected blood was significantly higher than in the control groups. Furthermore, the Hb levels were maintained at constant levels until the time of surgery. With an average dose of 200 IU of Eprex/kg b.w. twice weekly, patients awaiting elective surgery can not only increase the amount of predonated autologous blood collected but can also minimize the need of additional homologous transfusions thus preventing the development of anemia. In addition, a higher number of patients achieve the required amount of donated autologous blood for their operation.

Similar benefits can be seen in perioperative use of r-Hu EPO. The maximum rate of rise in Hct occurred after 2 days post surgery and was also significantly greater in the r-Hu EPO group and continued for a longer period of time. The recovery period to reach preoperative Hct was significantly shorter in the r-Hu EPO group, clearly indicating its positive effect. The use of Eprex in perisurgical settings remains to be determined in further clinical trials.

r-Hu EPO AND HEMATOLOGICAL INDICATIONS

In addition to the indications mentioned above, rHu EPO has potential in a variety of other conditions, especially within a field of hematology (Table 3).

The role of r-Hu EPO in these conditions is likely to be fully elucidated in the coming years. The major indications studied to date include:

1. Sickle cell anemia and β thalassemia

r-Hu EPO was chosen for the therapy because of its ability to stimulate the production of fetal Hb (HbF), a type of hemoglobin that does not enter into polymers of sickle cell hemoglobin. On going trials using 2000-3000 IU of r-Hu EPO/kg b.w. once or twice weekly indicate increase in HbF and F-reticulocyte,

Table 3. Future development of r-HuEPO
Current studies * anemia of chronic renal failure (predialysis and dialysis) * anemia of HIV/AZT therapy * anemia of cancer * facilitator of presurgical autologous blood prediposit * perisurgical adjuvant in elective surgical patients
Future indications * anemia of prematurity * sickle cell anemia * β thalassemia * anemia due to primary bone marrow disease * anemia of thermal injury * anemia of chronic inflammatory conditions

with no adverse effects of treatment shown. These trials show that the potential or r-Hu EPO to induce the production in both animals and humans exists. This may open new horizons in the therapy of SCA, however, studies are needed to determine the optimal dosage and parameters of the treatment. The recent study of combined r-Hu EPO and hydroxyurea treatment have been performed. The treatment of human thalassemia should aim to induce increased fetal Hb synthesis and reduce globin chain imbalance. The recent data indicate that r-Hu EPO treatment reduced membrane protein alterations of circulating thalassemic RBCs. The increase in Hb and Hct, changed β-globin chain synthesis and improved erythrocyte abnormalities were achieved.

2. Anemia of bone marrow diseases

The interest in possibility of r-Hu EPO to induce diminished erythropoiesis is still growing, especially when the safety use of even high doses of r-Hu EPO has been documented. Although the EPO deficiency is not a basis of anemia in myelodisplastic syndromes and aplastic anemia as well as hereditary hypoplastic anemia, one rationale for the use of r-Hu EPO comes from observations that patients have occasionally responded to androgens, which might augment the effect of EPO. Researchers hypothesized that residual stem cell or even the abnormal clone itself might respond to very elevated levels of EPO. The inadequate to the severity of anemia level of EPO is also discussed. The responding subset has not yet been defined and further work to define which patients will respond to therapy is required. The optional indciation would be a combined treatment with other cytokinins such as G or GM CSF and IL 3.

3. Supportive care

The combination of r-Hu EPO and other cytokinins to accelerate the restoration of hemopoiesis after high dose chemotherapy and especially bone

marrow transplantation are sometimes discussed in literature. The observations concerning erythroblastopenic potenital of G and GM CSF in mise and promising data, seem to establish the role of r-Hu EPO in BMT in the near future. Although the conclusions were based on a small and limited number of patients these data showed decreased need for erythrocyte transfusions, improved quality of life and increase in reticulocyte counts more rapid than in patients not receiving r-Hu EPO.

r-Hu EPO THERAPY – FINAL REMARKS

Therapy with r-Hu EPO is remarkably well tolerated by most patients, with few, if any, minor adverse reactions reported. Hypertension and seizures were reported in nephritic patients only, and were related, to the rapid increase in Hb and Hct. Even when the doses up to 3000 u/kg b.w./week were given, any of these effects have been noted. In patients with no-renal anemia the response to r-Hu EPO is quite heterogenous, depending on the underlying cause of anemia and additional, still undefined, factors. A summary of the factors that may be involved in the pathogenesis of partial or total resistance to the action of r-Hu EPO in uremic and in non-uremic patients is provided in Table 4.

Table 4. Modulating factors potentially involved in the hematopoietic response to EPO

iron deficiency
inflammatory states, infections, surgery
neoplastic diseases
aluminium intoxication
secondary hyperparathyroidism
vitamin deficiency states
hemolysis
uremic toxins
anephric state
rout of EPO administration

The most important of them is diminished iron stores or/and decreased availability of iron which causes relative resistance to r-Hu EPO treatment. Careful attention to the extent and rate of Hb correction, control of blood pressure and concomitant use of other drugs as well as the care with technical aspects of treatment of general conditions should reduce side effects to a minimum.

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STRESZCZENIE

Burzliwy w ostatnich latach, rozwój inżynierii genetycznej doprowadził do coraz śmielszego stosowania, uzyskanych poza ustrojem, naturalnych hormonów człowieka. Zastosowanie takich substancji nie tylko usprawnia leczenie chorób, ale rozszerza również naszą wiedzę o fizjologii ludzkiego organizmu. Podobnie stało się z erytropoetyną – pierwszym tak złożonym białkiem zastosowanym w terapii człowieka, a uzyskanym drogą rekombinacji genetycznej. Typowym już, bezdyskusyjnym dzisiaj wskazaniem dla podawania ludzkiej rekombinowanej erytropoetyny jest niedokrwistość towarzysząca niewydolności nerek. Poza korekcją niedokrwistości oraz unikaniem transfuzji krwi i towarzyszących im powikłań, przywraca ona chorym zdolność do normalnego życia. W niniejszej pracy omówiono natomiast podstawowe problemy oraz najnowsze wskazania do leczenia ludzką rekombinowaną erytropoetyną.